



## FORMULATION AND DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEM OF ANTIFERTILITY DRUGS USING COMBINATION OF POLYMERS.

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### ABSTRACT

The rising population of India is a cause of concern today. High population is a hurdle for nation development and growth. Although a large number of Contraceptives are available nowadays, but even today, there are concerns associated with them. Oral contraceptives have been widely linked with the cause of venous thrombosis and pulmonary emboli in women. Therefore, it was decided to investigate formulation and development of transdermal patch containing Ethinylestradiol (EE) and Medroxy progesterone acetate (MPA). The combination therapy of Ethinylestradiol (EE) and Medroxyprogesterone acetate (MPA) transdermal patch has shown efficacy in antifertility treatment. The present studies were designed to develop a suitable matrix type Transdermal Drug delivery system (TDDS) of EE and MPA using various polymers combinations. Nine formulations (F1-F9) were developed by varying the concentration of polymers HPMC, Ethylcellulose and Polyvinylpyrrolidone (PVP) and keeping the drug load constant. Propylene glycol (PG) was used as penetration enhancer. Physical parameters and drug excipient interaction studies were evaluated in all the formulations were simultaneously characterized in a thermostatically controlled modified Franz Diffusion cell. Based on physical parameters and *in vitro* skin permeation profile formulation F8 was found to be the best and chosen as final patch formulation for further studies. Stability profile of formulation F8 depicted stability up to 3 months. The Antifertility patch shows future potential for the further research and need of conduction of human clinical trials for further investigations.

**KEYWORDS:** *Ethinylestradiol, Medroxyprogesterone Acetate, Transdermal patch, Antifertility, Penetration Enhancers, Ethylcellulose, Polyvinylpyrrolidone*



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## INTRODUCTION

In the early 1960s, shortly after the introduction of oral contraceptives, the first case reports appeared describing venous thrombosis and pulmonary emboli in women using oral contraceptives as a method for birth control. Later, myocardial infarction and stroke were also found to be associated with the use of oral contraceptives. The absolute risk of venous thrombosis has been reported to increase from a baseline risk of less than 1 per 10,000 women-years to 3 to 4 per 10,000 women-years during use of Oral Contraceptives (OCs)<sup>1</sup>. Oral contraceptives containing estrogen-progestin combinations have been associated with an increased risk of deep vein thrombosis and subsequent pulmonary embolism, collectively referred to as venous thromboembolism (VTE)<sup>2-6</sup>. A large number of Transdermal Drug Delivery (TDD) systems have been widely used to treat a variety of diseases, since it has many advantages over oral contraceptive pills. TDD systems are able to provide continuous supply of drug through the skin, avoiding peaks and troughs as found with oral pills. Losses of bioavailability due to first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract that are seen with oral drug administration are avoided, which makes it possible to use lower doses of drug to achieve the therapeutic effect.<sup>7</sup> Postmenopausal HRT with oral or transdermal estrogen alone has been effective in alleviating vasomotor symptoms of menopause and also in reducing cardiovascular mortality risks and osteoporosis, but concomitant progestin therapy would protect against endometrial hyperplasia and carcinoma without compromising the benefits of estrogen therapy.<sup>8</sup> Therefore, it was decided to plan formulation and development of transdermal patch containing Ethinylestradiol (EE) and Medroxy progesterone acetate (MPA) using various polymers, permeation enhancers and plasticizers to overcome the side effects associated with oral contraceptives pills and have an alternative to the patients suffering from daily dosing problems associated with oral contraceptives.

## MATERIALS AND METHODS

### Materials

Ethinylestradiol was obtained as a gift sample from cipla pharmaceuticals, Ltd., Mumbai and Medroxyprogesterone acetate was obtained from Tokyo Chemical Industry Co., Ltd, Japan. HPMC, EC and PVP were obtained from Central Drug House Pvt. Ltd., New Delhi. Other materials used in the study (Sodium chloride, Disodium hydrogen phosphate, Potassium Dihydrogen phosphate etc) were purchased from Central Drug House Pvt. Ltd., New Delhi and were of analytical grade. Double Distilled water was used throughout the study.

### Simultaneous spectrophotometric determination of EE and MPA

Ethinylestradiol absorbs at  $\lambda_{max}$  of MPA and vice versa. Thus, a simple spectrophotometric method using no prior separation has been developed for the analysis of EE and MPA in phosphate buffer (pH 7.4) by Vierordt's equation<sup>9</sup>.

### Drug-polymer interaction studies

The physicochemical compatibility between the drugs and polymers used in the patches was studied by using differential scanning calorimetry (DSC). The sample was heated between 30°C and 300°C at the rate of 10°C/min in an atmosphere of nitrogen (20 mL/min). The thermograms obtained for the drug, polymers, physical mixture of drugs with polymers and formulation (patch) were compared.

### Preparation of films

The matrix transdermal patch containing EE and MPA was prepared using different polymers. Method used for the preparation of transdermal film is by solvent casting technique. Table 1 shows composition of transdermal films of EE and MPA with HPMC, EC & PVP. To prepare polymeric solution for transdermal film, required quantity of polymer was taken to obtain the concentration of 2% & 3% w/v. Polymer were dissolved in the ethanol with the help of magnetic stirrer for 30 min. Drug was dissolved separately in the solvents with help of magnetic stirrer for 30 min, propylene glycol (PG) was added to this drug solution and mixed with the help of magnetic stirrer for another 30 min. The solution containing drug with PG was added to the polymer solution and the whole solution was stirred for 30 min using magnetic stirrer. Then the solution was sonicated to ensure the uniform distribution, and then the solution was casted in flat surfaced petridish. The casting volume was kept as 5 ml/ 2 cm<sup>2</sup> to get the drug concentration of 7 mg/ 2cm<sup>2</sup>. The films were dried at room temperature, to avoid rapid evaporation of solvent and the drug, the petridish was covered with the inverted funnel for 48 h. The dried films were taken out and packed in an aluminium foil covering, which was used as backing membrane. The dried films were stored in desiccators for a week until further evaluation. There was no change in the physical appearance or texture of the films after storage.

### Physicochemical Evaluation of the prepared transdermal patch.<sup>10,13</sup>

#### Organoleptic Characteristics

The prepared patch was physically inspected for its appearance, colour, clarity, flexibility, and smoothness.

#### Thickness

The thickness of the patches was assessed at three different points using screw gauze and the average weight of three patches was calculated.

#### Weight Uniformity

Three patches of equal size were taken and weighed on electronic balance to check for weight variation

#### Folding Endurance

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance<sup>10</sup>

#### Moisture Content

The prepared patch was weighed and kept in the dessicator containing fused calcium chloride for about 24 hours. After that it was taken out and weighed

again<sup>10</sup>. The percentage of moisture content was calculated on the basis of the following formula

$$\text{Percentage of moisture content} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100.$$

#### **Drug Content Determination<sup>13</sup>**

The patch (1 cm<sup>2</sup>) was cut and added to a beaker containing 100 ml of phosphate buffered pH 7.4. The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whatman filter paper and the filtrate was analyzed by U.V. spectrophotometer at 280 nm for the drug content against the blank solution.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

#### **In vitro drug release studies<sup>11,13</sup>**

The *in vitro* release was carried out with the semi permeable membrane using open ended cylinder. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5 °C and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). The drug containing patch with a support of backing membrane was kept in the donor compartment and it was separated from the receptor compartment by semipermeable membrane. The semipermeable membrane was previously soaked for 24 hours in phosphate buffer (pH 7.4). The receptor compartment containing 300 ml phosphate buffer (pH 7.4) in a beaker was maintained at 37 ± 0.5 °C and stirred at 50 rpm with magnetic beads operated by magnetic stirrer. A sample of 1 ml was withdrawn at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by spectrophotometrically at 280 nm.

#### **Ex vivo Skin Permeation Studies<sup>11,13</sup>**

The *in vitro* skin permeation studies were carried out using dorsal section of full thickness skin from albino rats (weighing between 200-250 g) whose hair had been removed. The transdermal patches were firmly pressed on the centre of the rat skin. Once adhesion to the skin surface had been confirmed, the skin was quickly mounted on the diffusion tube which acted as the donor compartment. 100 ml of phosphate buffer of pH 7.4 taken in a beaker, which acted as the receptor compartment to maintain the sink condition. The donor compartment was kept in contact with the receptor compartment and the receptor compartment was stirred magnetically during the study. After every 1 hrs sample (1ml) was withdrawn at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by U.V. spectrophotometrically at 240 nm.

## **RESULTS AND DISCUSSION**

#### **Organoleptic Characteristics.**

The prepared patches were translucent showing good flexibility and smoothness.

#### **Moisture Absorption<sup>13</sup>**

The films were placed in dessicator containing saturated solution of aluminum chloride, keeping the humidity inside the dessicator at 79.5% RH. After 3 days the films were taken and weighed the percentage moisture absorption of three films were determined.

#### **Thickness.**

The thickness of prepared patches was ranged between 0.024 ± 0.002mm to 0.026 ± 0.006 mm as given in Table 2.

#### **Weight Uniformity.**

The weight of prepared patches was ranged between 25.83±0.17 mg to 26.87±0.18 mg as given in Table 2. The weights are found to be high with films prepared with higher proportions of HPMC.

#### **Folding Endurance.**

The folding endurance of prepared patches was ranged between 95 ± 2.4 to 127 ± 2.4 as given in Table 2.

#### **Moisture Content.**

The moisture content of prepared patches was ranged 1.983 ± 0.013 % to 2.642 ± 0.056 % as given in Table 2.

#### **Moisture Absorption**

The moisture absorption of prepared patches was ranged between 2.316 ± 0.011 % to 2.802 ± 0.026 as given in Table 2.

#### **Drug Content**

The drug content of the prepared patches was ranged between 96.38 ± 0.10 mg to 97.69 ± 0.12 in w/w ratio with the weight of patch as given in Table 2. Good Uniformity in drug content was observed.

#### **In Vitro Release studies**

Release rate was increased when the concentration of HPMC was increased in the content of the polymer in the formulations. The cumulative percentage release from the various formulations are shown in Table 3. This is because as the proportion of this polymer in the matrix increased, there was an increase in the amount of water uptake and hydration of the polymer matrix and thus more drugs was released. The EC was used to retard the release of the drug from the matrix due to the more hydrophobic nature; therefore the prolonged drug release was obtained. The results of the *in vitro* drug release studies from transdermal patches were showed in Fig 1.

#### **Ex vivo skin permeation studies**

The results of *ex vivo* permeation of EE and MPA from patches are shown in Table 3. The order of drug permeation from different formulations was increased in

the following order: F-8>F-5>F-9>F-3>F-7>F-6>F-2>F-1>F-4. The results corroborated that higher the drug release from the formulation, higher was the rate and extent of drug permeation. Percent drug release from the formulation F-8 was higher than other leading to conclusion that HPMC and PVP combination is better than individual polymer as the polymeric precursor for the EE and MPA transdermal patches. As the concentration of hydrophilic polymer was increased, the amount of drug permeated was increased. This may be a result of the initial rapid dissolution of the hydrophilic polymers when the patch is in contact with the hydrated skin, which results in accumulation of high amounts of drug on the skin surface and thus leads to the saturation of the skin with drug molecules at all times<sup>12</sup> The patches containing higher amounts of Ethylcellulose (EC) were having less drug release, which can be attributed to its hydrophobic properties. Due to hydrophobic nature, thermodynamic activity is reduced

and which further results in decrease of drug release. Comparison between all the formulations revealed that extent of drug release was higher in case of (polymers HPMC and PVP in combination) than (polymers HPMC, EC and PVP without combination). The higher drug release from formulation F8 is due to higher permeability characteristics of HPMC as compared to EC. Propylene glycol (PG) acts as a penetration enhancer due to its co solvency effect, PG partitions when entering into the skin and enhances the movement of the drug molecules into the skin. The thermodynamic activity of the PG propels this enhancement activity. PG acts meticulously in the transport of drug molecules across the skin. It is evident that all the formulations F1-F9 followed Higuchi kinetics, as the regression coefficients ( $r^2$ ) values for the release of both EE and MPA are closer to 1 (Table 4) and more than the ( $r^2$ ) values obtained after treating the data through zero order or first order kinetics.

**Table 1**  
**Composition of EE and MPA Transdermal Drug Delivery systems.**

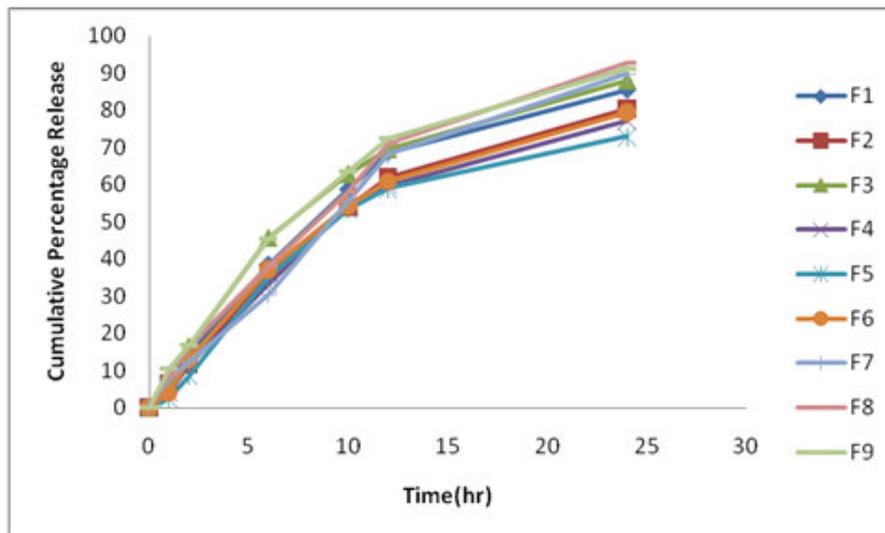
Formulation Code	Polymers			Plasticizer		Drug	Drug
	HPMC:EC % W/V	EC:PVP % W/V	HPMC:PVP % W/V	PG % w/w	DMSO % w/w	EE (mg/cm <sup>2</sup> )	MPA (mg/cm <sup>2</sup> )
F1	0.5:1.5	-	-	30	7	0.35	2.14
F2	1:1	-	-	30	7	0.35	2.14
F3	1.5:0.5	-	-	30	7	0.35	2.14
F4	-	0.5:1.5	-	30	7	0.35	2.14
F5	-	1:1	-	30	7	0.35	2.14
F6	-	1.5:0.5	-	30	7	0.35	2.14
F7	-	-	0.5:1.5	30	7	0.35	2.14
F8	-	-	1:1	30	7	0.35	2.14
F9	-	-	1.5:0.5	30	7	0.35	2.14

EC: ethyl cellulose, PVP: polyvinylpyrrolidone, HPMC: hydroxypropyls methylcellulose, PG: propylene Glycol, DMSO: Dimethyl sulfoxide

**Table 2**  
**Physicochemical parameters of transdermal patches (F1-F9)**

Sr. No	Formulation Code	Mean Thickness (mm)	Moisture Content (%)	Moisture Absorption (%)	Drug Content (%)	Folding Endurance	Weight (mg)	Tensile strength (gm/10cm <sup>2</sup> )	Moisture absorption (%)	Water vapour transmission rate Gm/cm <sup>2</sup> /72 hrs
1	F1	0.026 ±0.002	2.134 ± 0.010	2.574 ±0.023	96.54 ±0.36	105 ±2.6	26.43±0.16	15.13 ±0.23	2.574 ±0.023	0.01680 ±0.002
2	F2	0.026 ±0.006	1.983 ±0.013	2.321 ±0.011	96.55 ±0.24	95 ±2.4	26.87±0.18	14.96 ±0.35	2.321 ±0.011	0.01676 ±0.005
3	F3	0.025 ±0.005	2.506 ±0.024	2.643 ±0.021	96.87 ±0.28	102 ±5.6	26.50±0.16	15.44 ±0.17	2.643 ±0.021	0.01692 ±0.006
4	F4	0.025±0.004	2.628 ±0.021	2.632 ±0.016	98.45 ±0.27	110 ±4.9	26.22±0.17	15.36 ±0.27	2.632 ±0.016	0.01706 ±0.003
5	F5	0.024 ±0.002	2.632 ±0.010	2.528 ±0.015	97.29 ±0.75	119 ±5.2	25.95±0.26	15.58 ±0.12	2.528 ±0.015	0.01704 ±0.002
6	F6	0.026 ±0.003	2.114 ±0.021	2.528 ±0.015	96.26 ±0.84	111 ±3.7	26.88±0.14	14.32 ±0.27	2.316 ±0.011	0.01694 ±0.005
7	F7	0.025 ±0.003	2.598 ±0.014	2.316 ±0.011	97.45 ±0.21	124 ±5.9	25.98±0.15	14.89 ±0.14	2.802 ±0.026	0.01717 ±0.003
8	F8	0.025 ±0.002	2.642 ±0.056	2.802 ±0.026	97.69 ±0.12	127 ±2.4	25.83±0.17	15.86 ±0.10	2.864 ±0.027	0.01720 ±0.002
9	F9	0.026 ±0.002	2.31 ±0.024	2.624 ±0.025	96.38 ±0.10	116 ±2.8	26.34±0.16	15.64 ±0.11	2.624 ±0.025	0.01718 ±0.002

Results = Mean ± SD ; n=3



**Figure 1**  
**Drug Release profiles of EE and MPA from formulations F1-F9**

**Table 3**  
**Drug Release profile of EE and MPA formulations F1 to F9 with different polymer combination.**

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.96 ± 2.36	7.05 ± 5.86	7.85 ± 6.91	6.85 ± 10.68	7.31 ± 10.37	5.23 ± 8.32	6.68 ± 10.23	7.58 ± 8.65	6.89 ± 11.32
2	12.36 ± 5.89	13.04 ± 5.65	14.34 ± 10.36	12.10 ± 9.63	12.36 ± 11.31	8.65 ± 10.35	10.32 ± 9.35	12.35 ± 8.32	16.23 ± 5.94
6	37.12 ± 8.67	34.86 ± 12.67	39.01 ± 11.67	37.45 ± 7.62	47.58 ± 2.98	36.57 ± 2.36	32.42 ± 12.23	40.23 ± 5.39	42.12 ± 11.02
10	54.84 ± 10.26	55.20 ± 10.65	59.21 ± 10.39	54.24 ± 9.37	62.52 ± 9.67	54.52 ± 10.36	50.22 ± 10.46	62.53 ± 8.32	60.23 ± 7.36
12	60.10 ± 12.34	60.45 ± 10.65	69.31 ± 2.98	59.89 ± 7.38	71.02 ± 6.97	61.98 ± 11.84	62.78 ± 9.65	68.94 ± 7.64	70.98 ± 8.36
24	77.96 ± 2.12	78.46 ± 4.23	85.64 ± 5.23	77.27 ± 1.14	88.62 ± 2.35	80.83 ± 3.65	85.21 ± 2.25	88.94 ± 1.15	87.73 ± 2.13

**Table 4**  
**Regression Coefficient ( $r^2$ ) values of kinetic model of formulation F1-F9**

Formulation code	Zero order Regression value ( $R^2$ )	First order Regression value	Higuchi Regression value	KoresmeyerPeppas (slope)
F1	0.987	0.936	0.923	0.985
F2	0.932	0.934	0.923	1.206
F3	0.938	0.931	0.937	1.022
F4	0.936	0.935	0.922	1.024
F5	0.949	0.934	0.944	1.023
F6	0.934	0.931	0.926	1.024
F7	0.947	0.932	0.942	1.031
F8	0.950	0.935	0.945	0.985
F9	0.938	0.934	0.935	1.024

## CONCLUSION

Hydroxy propyl methylcellulose and Ethyl cellulose transdermal patches were found to have prolonged release of the drugs Ethinylestradiol and Medroxyprogesterone acetate. A slow and controlled release of the drugs was indicated by the plot of the drug release against square root of time, which was found to be linear, thus, supporting transdermal film formulation. This delivery of the combined formulation has been found to be beneficial since there has been no interaction between the drugs and the polymers. UV estimation of both the drugs in combination is possible using Vierordt's equation, and therefore these drugs can

be formulated as a sustained release drug delivery system. Further, in vivo studies have to be performed to correlate with in vitro release data. Further work is necessary in human volunteers to confirm the pharmacokinetic and pharmacodynamics evaluation.

### Future Prospects

The future prospects lies in the testing of the developed patch for further studies in animals for pharmacodynamics and toxicologic profile. Since the presence of only progesterone causes escape /tolerance phenomenon (as per WHO recommendation) and Endometrial carcinoma. Therefore, combination of estrogen and progesterone are taken for adequate

efficacy, sustainability, avoidance of the harmful effects of only progesterone. It is clear to understand the need for further investigation and study of newer combinations of estrogen and progesterone to develop a transdermal patch having high efficacy of fertility control and improved compliance. This system may also prove to be useful in Hormonal Replacement Therapy (HRT). From this study proposal, it is envisaged that the transdermal patch will show sustained drug plasma levels and the most important benefit is that it is noninvasive technique, which is easy to terminate by removing the patch from the site and most importantly it improves the patient compliance.

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## CONFLICT OF INTEREST

Conflict of interest declared none.

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